Phase 1b Study of the Selective BRAF V600 Inhibitor Encorafenib (LGX818) Combined With Cetuximab With or Without the α-specific PI3K Inhibitor Alpelisib (BYL719) in Patients With Advanced BRAF-mutant Colorectal Cancer

Disclosures

- Investigator on phase 1 & 2 studies ([www.nki.nl](http://www.nki.nl))
- Member Dutch Medicines Evaluation Board
- Chairperson SAG-Oncology EMA
- Inventor on patents:
  - Enabling oral docetaxel and paclitaxel therapy
  - Improving oral bioavailability of a.o. Top I inhibitors
  - Improving brain uptake of a.o. imatinib
  - Assessing activity of PARP inhibitors in PBMCs
- Consultancy fees from industry to NKI
- No off label use will be presented
**BRAF V600E and BRAFm-like CC tumors have poor outcome vs non-BRAFm-like tumors**

CC, colon cancer; pred-BRAFm, predicted to be BRAF mutant; pred-BRAFwt, predicted to be BRAF wild type.

Vemurafenib response rate in *BRAF* mutant melanoma vs colon cancer

From synthetic lethal shRNA screen to synergistic response of \textit{BRAFm} CRC to EGFR and BRAF inhibition \textit{in vitro} and \textit{in vivo}\textsuperscript{1,2}

CON, control; ERL, erlotinib; VEM/PLX/PLX4032, vemurafenib.

Negative feedback regulation of EGFR disappears upon BRAF inhibition in BRAFm CRC

CRC, colorectal cancer.
Clinical phase 1/2 study in patients with metastatic BRAFm colorectal cancer

Phase 1b Dose Escalation
BRAFm metastatic CRC (n ≈ 24)

Stage 1 - Dual Combination
- Molecular Pre-screening
- Encorafenib + Cetuximab → MTD/RP2D (dual)

Phase 2
BRAFm metastatic CRC (n ≈ 100)

Molecular Pre-screening
Randomization

- Encorafenib + Cetuximab
  - MTD/RP2D (dual)
  - n ≈ 50
- Encorafenib + Alpelisib + Cetuximab
  - MTD/RP2D (triple)
  - n ≈ 50

Vehicle
Encorafenib 20mg/kg QD
Cetuximab 20mg/kg biweekly
Paclitaxel

1:1 Pair-wise combinations

Triple combination
Single agent treatments

BID, twice daily; MTD, maximum tolerated dose; QD, once daily; RP2D, recommended phase 2 dose.
Study objectives

• **Primary**
  – Phase 1: Determine MTD/RP2D

• **Secondary**
  – Characterize safety and tolerability
  – Assess antitumor activity
  – Determine pharmacokinetic profile of encorafenib ± alpelisib

• **Exploratory**
  – Explore genetic determinants of response
  – Explore potential mechanisms of resistance

MTD, maximum Tolerated Dose; RP2D, Recommended Phase II dose
Eligibility criteria – phase 1b

Key Inclusion Criteria

- Adults ≥ 18 years of age
- KRAS wild type, BRAF-mutant mCRC\(^a\)
- ECOG PS 0-2
- Disease progression after ≥ 1 prior standard of care regimen or intolerance to irinotecan-based regimens
- Life expectancy ≥ 3 months

Key Exclusion Criteria

- Symptomatic brain metastases
- Hematologic parameters
  - Absolute neutrophil count < 1,500/mm\(^3\)
  - Platelets < 100,000/mm\(^3\)
  - Hemoglobin < 9.0 g/dL

\(^a\) A majority of patients had BRAF V600–mutant disease; however, 2 patients harbored non-V600 BRAF mutations.

ECOG PS, Eastern Cooperative Oncology Group performance status.
Dose escalation overview

Dual combination\(^a\)

- Encorafenib 450 mg QD + Cetuximab, n = 8
- Encorafenib 400 mg QD + Cetuximab, n = 9
- Encorafenib 200 mg QD + Cetuximab, n = 7
- Encorafenib 100 mg QD + Cetuximab, n = 2

1 DLT: grade 3 QTC prolongation
1 DLT: grade 3 vomiting
1 DLT: grade 3 arthralgia

Triple combination\(^a\)

- Encorafenib 200 mg QD + Cetuximab, n = 10
- Encorafenib 300 mg QD + BYL719 200 mg QD + Cetuximab, n = 7
- Encorafenib 200 mg QD + BYL719 200 mg QD + Cetuximab, n = 8
- Encorafenib 200 mg QD + BYL719 100 mg QD + Cetuximab, n = 3

1 DLT: grade 4 increased creatinine
1 DLT: grade 3 bilateral interstitial pneumonitis

- MTDb was not reached for either treatment combination

\(^a\) Cetuximab fixed dose across all dose-levels: loading dose 400 mg/m\(^2\); weekly dose 250 mg/m\(^2\)

\(^b\) Defined as the highest dose at which probability of DLTs are not expected to exceed 35% in the first treatment cycle.
## Patient disposition

<table>
<thead>
<tr>
<th></th>
<th>ENC + CTX (n = 26)</th>
<th>ENC + ALP + CTX (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients treated, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment discontinued</td>
<td>24 (92.3)</td>
<td>22 (78.6)</td>
</tr>
<tr>
<td>Treatment ongoing</td>
<td>2 (7.7)</td>
<td>6 (21.4)</td>
</tr>
<tr>
<td>Primary reason for treatment discontinuation, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>3 (11.5)</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (3.8)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>18 (69.2)</td>
<td>19 (67.9)</td>
</tr>
<tr>
<td>Physician decision</td>
<td>1 (3.8)</td>
<td>0</td>
</tr>
<tr>
<td>Patient decision</td>
<td>1 (3.8)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data cutoff date: February 1, 2015.

ALP, alpelisib; CTX, cetuximab; ENC, encorafenib.
## Patient demographics

<table>
<thead>
<tr>
<th></th>
<th>ENC + CTX (n = 26)</th>
<th>ENC + ALP + CTX (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>15 (57.7)</td>
<td>18 (64.3)</td>
</tr>
<tr>
<td>Male</td>
<td>11 (42.3)</td>
<td>10 (35.7)</td>
</tr>
<tr>
<td><strong>Age, median (range), years</strong></td>
<td>63 (43-80)</td>
<td>59 (40-76)</td>
</tr>
<tr>
<td><strong>Primary site of cancer derived, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>24 (92.3)</td>
<td>25 (89.3)</td>
</tr>
<tr>
<td>Rectum</td>
<td>2 (7.7)</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8 (30.8)</td>
<td>18 (64.3)</td>
</tr>
<tr>
<td>1</td>
<td>16 (61.5)</td>
<td>10 (35.7)</td>
</tr>
<tr>
<td>2</td>
<td>2 (7.7)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Visceral involvement at baseline, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>15 (57.7)</td>
<td>16 (57.1)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>5 (19.2)</td>
<td>8 (28.6)</td>
</tr>
</tbody>
</table>

Data cutoff date: February 1, 2015.
ALP, alpelisib; CTX, cetuximab; ENC, encorafenib.
### Adverse Events Suspected to be Drug Related

<table>
<thead>
<tr>
<th>Adverse Event (AE), n (%)</th>
<th>ENC + CTX (n = 26)</th>
<th>ENC + ALP + CTX (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Total</td>
<td>21 (80.8)</td>
<td>6 (23.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (26.9)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (7.7)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>4 (15.4)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1 (3.8)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (23.1)</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>Dermatitis acneiform</td>
<td>2 (7.7)</td>
<td>0</td>
</tr>
<tr>
<td>Dry skin</td>
<td>4 (15.4)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (42.3)</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>3 (11.5)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>5 (19.2)</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>1 (3.8)</td>
<td>0</td>
</tr>
<tr>
<td>Melanocytic nevus</td>
<td>1 (3.8)</td>
<td>0</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>6 (23.1)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data cutoff date: February 1, 2015.
ALP, alpelisib; CTX, cetuximab; ENC, encorafenib.
Antitumor activity
Best radiological response

Data cutoff date: February 1, 2015.

* Patients treated at the RP2D.  • MSI  ○ MSS

Dual Combination
PD: 4 (15%)
SD: 14 (54%)
PR: 5 (19%)a
CR: 1 (4%)

Triple Combination
PD: 1 (4%)
SD: 17 (61%)
PR: 9 (32%)b

a Includes 1 unconfirmed PR.
b Includes 4 unconfirmed PRs.
## Best overall response

<table>
<thead>
<tr>
<th>Response</th>
<th>ENC + CTX (n = 26) n (%)</th>
<th>ENC + ALP + CTX (n = 28) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>1 (3.8)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>5 (19.2)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9 (32.1)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>14 (53.8)</td>
<td>17 (60.7)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>4 (15.4)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (7.7)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Overall response rate (CR + PR)</td>
<td>6 (23.1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9 (32.1)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Disease control rate (CR + PR + SD)</td>
<td>20 (76.9)</td>
<td>26 (92.8)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes 1 unconfirmed PR.

<sup>b</sup> Includes 4 unconfirmed PRs.

Data cutoff date: February 1, 2015.

ALP, alpelisib; CTX, cetuximab; ENC, encorafenib.
Antitumor activity
Time on study, by response—Dual combination

Data cutoff date: February 1, 2015.
Antitumor activity

Time on study, by response—Triple combination

Duration of exposure, weeks

- Partial response (PR)
- Stable disease (SD)
- Progressive disease (PD)
- Unknown
- Ongoing

Data cutoff date: February 1, 2015.
Progression-free survival—All patients

Data cutoff date: February 1, 2015.

ALP, alpelisib; CTX, cetuximab; ENC, encorafenib.
Results
Exploratory endpoint—potential mechanisms of resistance

Baseline
• Patient 1401003

Mutation analysis: primary tumor
Tested:
Hotspots in AKT1, AKT2, BRAF, CDK, EGFR, ERBB2, FGFR1, FGFR3, FLT3, HRAS, JAK2, KIT, KRAS, MET, NRAS, PDGFRA, PIK3CA, RET
→ BRAF V600E

• Start study treatment: cetuximab + encorafenib

• Confirmed PR after 10 weeks

After 4 months of therapy: New progressive lesion
Mutation analysis: new lesion (same gene panel):
→ BRAF V600E and KRAS G12R
Biomarker analysis

- Gene alterations with roles in CRC development (eg, WNT\textsuperscript{1}) or relationships with \textit{BRAF} mutations (eg, MSI\textsuperscript{2}) may correlate with clinical outcome

- Somatic mutation calls, LOH, and CN aberrations for 22 samples were called by Foundation Medicine assay analytics
  - Tumor purity and ploidy reflected in confidence for mutation and CN calls
  - Additional annotations from COSMIC used to filter functional mutations

- Several key pathways (MAPK, PI3K, WNT/β- catenin, and EGFR), along with MSI status, were investigated

- Biomarker data were included in the efficacy analyses

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CN, copy number; LOH, loss of heterozygosity; MSI, microsatellite instability; MSS, microsatellite stable.

Efficacy vs genetic alterations by combination regimen

**Patients treated at the RP2D.**

Data cutoff date: February 1, 2015.

* Single-base substitutions, short insertions and deletions.
PFS vs genetic alterations and allele frequency by gene pathways

Data cutoff date: February 1, 2015.
PFS vs LOH, CN, and ploidy for *BRAF* patients

Data cutoff date: February 1, 2015.

* Patient with non-V600 mutation (598R).
Conclusions

- Both the dual and triple combinations were well tolerated.
- The dual and triple combination arms had similar ORR (23.1% vs 32.1%) and median PFS (3.7 vs 4.2 months).
- MTD was not reached for either combination; established RP2Ds were:
  - Dual combination: 200 mg encorafenib QD + cetuximab QW
  - Triple combination: 200 mg encorafenib QD + 300 mg alpelisib QD + cetuximab QW
- Mutational analyses showed that:
  - PI3K activation did not correlate with response.
  - \textit{BRAF} amplification appears to correlate with longer PFS.
  - There was no clear relationship between MAPK pathway activation and mutations related to WNT signaling (eg, APC) and PFS.
- Enrollment into the phase 2 portion of the study is ongoing.
- Combined EGFR and BRAF +/- PIK3CA inhibition may become the new standard of care in advanced \textit{BRAFm} metastatic CRC.
Acknowledgments

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- The authors are grateful for the support from Professor René Bernards, Netherlands Cancer Institute, Amsterdam, NL.